ijtos 2024; doi 10.22376/ijtos.2024.2.4.1-6

International Journal of Trends on OncoScience

ISSN-2583-8431

Review Article

Exploring Autophagy in Cancer: Therapeutic Perspectives

Dr. Anand Mohan Jha[1], Dr. Anil Kumar[2], Dr. Kumud Kumari[3], Dr. Rashmi Hosamani[4], Dr. S. Ravichandran[5], Dr. Vanitha Innocent Rani[6] and Dr Priyanka Singh[7*]

1Post Graduate Department of Chemistry, M. L. S. M. College, Darbhanga, (Lalit Narayan Mithila University, Darbhanga, Bihar)

2Post Graduate Department of Chemistry, Sahibganj College, Sahibganj (S. K. M. University, Dumka, Jharkhand)

3Department of Psychology, MLSM College, Darbhanga (Lalit Narayan Mithila University, Darbhanga, Bihar)

4Associate Professor, Department of Microbiology, Tumkur University, Karnataka

5Professor and Head in Chemistry, DRK Institute of Science and Technology, Bowrampet, Hyderabad-500043.

6 Assistant professor, Department of community & Psychiatric Nursing, Faculty of Nursing, King Khalid University, Mahayil, Asir Region, KSA.

*7*Additional Professor, Department of Oral Pathology and Microbiology, Faculty of Dental Sciences, King George's Medical University, Lucknow*

Abstract: Autophagy is a catabolic mechanism crucial for sustaining cellular homeostasis, and in this process, encapsulated degraded inside repurposed to facilitate metabolic processes. In cancer, autophagy has a dual role: it acts as a tumor suppressor by preventing the buildup of damaged cellular components, but also as a survival mechanism, that supports tumor growth under stress. Cancer cells often trigger autophagy to manage the increased metabolic demands of rapid growth. This stress tolerance allows tumor cells to maintain energy production, contributing to both tumor progression and resistance to treatment. Preclinical studies have shown that autophagy inhibition reinstates chemotherapeutic sensitivity and increases tumor cell mortality. These findings indicate that targeting autophagy may represent a viable therapeutic approach, with early-phase clinical trials exploring the use of hydroxychloroquine alongside chemotherapy or targeted treatments. As comprehension of autophagy in oncology advances, there is an increasing interest in creating more targeted and efficacious autophagy inhibitors for therapeutic applications.

Key words: Autophagy, Cancer, Tumor Suppression, Chemo resistance, Therapeutic Target, Hydroxychloroquine.

***Corresponding Author**

Dr Priyanka Singh , Additional Professor, Department of Oral Pathology and Microbiology, Faculty of Dental Sciences, King George's Medical University, Lucknow

Received On 28 June 2024
Revised On 28 August 2024
Accepted On 4 September 2024
Published On 1 October 2024

Funding This review did not receive any specific grant from any funding agencies in the public, commercial or not for profit sectors.

Citation Dr. Anand Mohan Jha,Dr. Anil Kumar,Dr. Kumud Kumari,Dr. Rashmi Hosamani,Dr. S. Ravichandran,Dr.Vanitha Innocent Rani and Dr Priyanka Singh , Exploring Autophagy in Cancer: Therapeutic Perspectives.(2024).Int. J. Trends in OncoSci.2(4), 1-6 http://dx.doi.org/10.22376/ijtos.2024.2.4.1-6

1. INTRODUCTION

Macroautophagy, sometimes termed autophagy, is an essential and conserved cellular mechanism that maintains homeostasis by digesting organelles and proteins, hence maintaining cellular survival amid food scarcity or metabolic stress.[1] The process starts by the production of double-membrane vesicles termed autophagosomes, which enclose cytoplasmic materials. Autophagosomes fuse with lysosomes, facilitating the degradation and reutilization of their contents. Autophagy is crucial for the elimination of damaged or senescent cellular constituents across all cell types.[2] Impaired autophagy correlates with increased susceptibility to metabolic stress, DNA damage, and cancer in animal models, highlighting its function in tumor inhibition. Monoallelic loss of Beclin 1, a critical autophagy gene, has been seen in 40–75% of human breast and prostate cancers, and ovarian malignancies, indicating a protective role function of autophagy against tumor formation[3]. However, while autophagy may prevent tumorigenesis, it can also provide cancer cells with the resilience to survive harsh conditions. Tumor cells, especially in hypoxic regions, activate autophagy to meet the increased metabolic demands of rapid growth. This stress-induced autophagy can contribute to treatment resistance, tumor dormancy, and eventual recurrence. In preclinical studies, blocking survival-driven autophagy through genetic or pharmacological methods induced tumor cell death and apoptosis were reported. Combining autophagy inhibitors with chemotherapy significantly slowed tumor growth and promoted cell death more effectively than chemotherapy alone[4]. These findings suggest that survival-promoting autophagy could hinder cancer treatment, establishing it as a possible therapeutic target. Autophagy has a dual function; in some instances, excessive or extended autophagy may result in cellular demise, especially in apoptosis-resistant cells. Comprehending the function, the significance of autophagy in cancer therapy is paramount, since several anticancer medicines are recognized to induce autophagy, but the precise effects of this induction remain ambiguous. As the function of autophagy in cancer becomes more intricate, it is important to further explore how autophagy influences cancer development and treatment outcomes[5].

2. AUTOPHAGY REGULATION

Autophagy involves the formation of autophagosomes that enclose injured organelles or cellular debris, which then fuse with lysosomes to destroy their contents. Upon the formation of autophagosomes, the majority of Atg proteins revert to the cytoplasm, with the exception of a minor fraction of LC3-II that persists on the inner membrane[6]. LC3-II remains on mature autophagosomes until lysosomal fusion occurs, making it a common marker for autophagy. LC3-II also interacts with p62/sequestosome1 (SQSTM1), which aids in delivering ubiquitinated protein aggregates to the autophagic apparatus. During the progression of autophagy, p62/SQSTM1 undergoes degradation; however, its levels rise when autophagy is compromised, as seen in autophagy-deficient animals[7]. Subsequent phases of autophagy include the maturation and the formation of autophagosomes and their subsequent fusion with lysosomes to create autolysosomes, a process necessitating small Rab GT Pases lysosome-associated membrane protein 2[8]. The mTOR pathway, comprises mTORC1 and mTORC2 complexes a key regulator of autophagy[9]. Cellular strain inhibits mTOR1 activity, hence initiating autophagy. mTOR suppresses autophagy by phosphorylating Atg13, therefore disrupting its interaction with ULK1 and compromising development. the ULK1-Atg13 complex is important for the assembly of autophagosomes[10]. Reduced intracellular energy levels stimulate AMP-activated protein kinase (AMPK) and serves as a vital metabolic sensor that governs lipid and glucose metabolism. AMP-activated protein kinase activation inhibits mTOR and initiates autophagy, and recent studies suggest that AMPK directly phosphorylates ULK1, plays an essential role in mitochondrial function and cellular viability during fasting[11]. Hypoxia, via activating AMPK, also stimulates autophagy via HIF and its target gene BNIP3[12].

3. ROLE OF AUTOPHAGY IN TUMOR SUPPRESSION

Autophagy is an essential homeostatic process that, when disrupted, may promote the initiation and progression of cancer. It operates as a tumor suppressor by removing damaged organelles and proteins, therefore preventing uncontrolled cell proliferation and genetic instability. The Beclin 1 protein is crucial for the commencement of autophagy studies and have shown that animals with reduced Beclin 1 expression (Beclin $1^{+/-}$) have a higher susceptibility to tumors, indicating Beclin 1 operates as a haploin sufficient tumor suppressor[13]. Conversely, excessive activation overexpression of Beclin 1 may impede tumor development via autophagy. Studies demonstrate that the suppression of p62/SQSTM1 occurs in autophagy-deficient conditions cells reduces ROS levels and the corresponding DNA damage response[14]. Furthermore, studies indicated that animals deficient in p62/SQSTM1 exhibited protection against Ras-induced pulmonary cancers in contrast to wild-type mice[15]. Autophagy may also aid in cancer prevention by diminished necrosis and chronic inflammation are linked to the synthesis of the proinflammatory protein HMGB1[16]. Collectively, these data stresses the significance of autophagy as a tumor-suppressive mechanism. Key tumor suppressor genes, such as TP53 and PTEN, regulate this process, with proteins like Beclin-1 (BECN1) initiating autophagy17. The mTOR pathway inhibits autophagy in nutrient-rich conditions, but its dysregulation is often seen in cancer. Autophagy markers like LC3 are essential for autophagosome formation and cargo degradation, while p53 has a dual role in regulating autophagy. AMPK promotes autophagy during energy stress by inhibiting mTOR, and proteins like BNIP3 induce autophagy under hypoxic conditions. The PI3K-Akt pathway, often overactivated in cancer, negatively regulates autophagy. Dysfunction in Atg genes, which are vital for the autophagic process, or the lysosome, where cargo is degraded, can lead to cancer progression18. Autophagy and apoptosis are interconnected, with excessive or impaired autophagy potentially leading to programmed cell death, further contributing to tumor suppression.

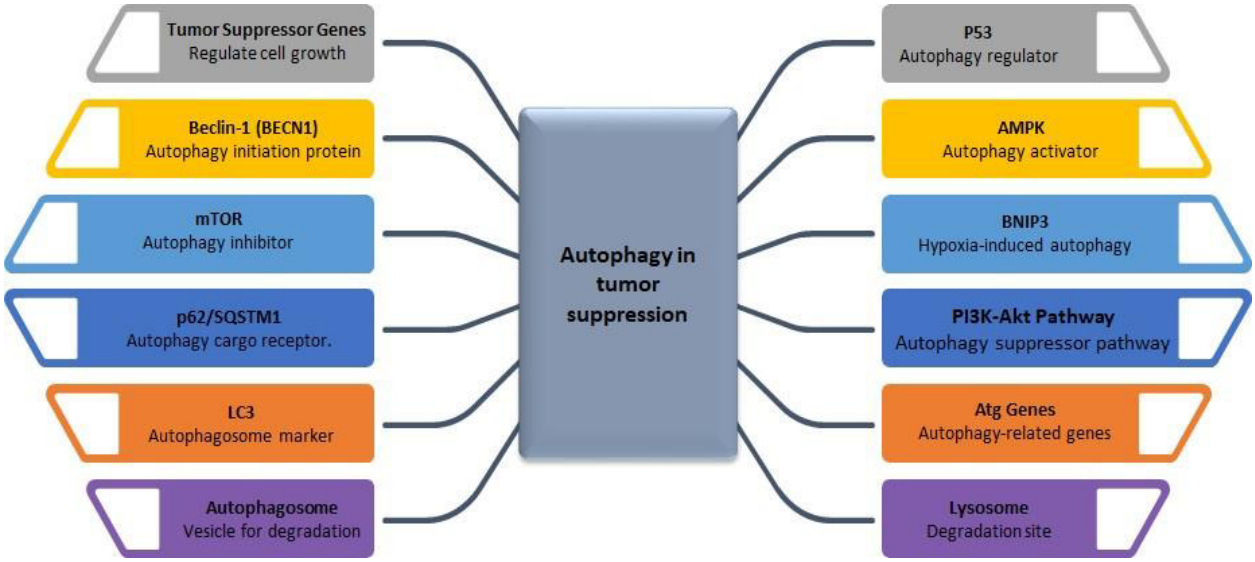

Fig 1: Autophagy in tumor suppression

4. ROLE OF AUTOPHAGY IN TUMOR CELL SURVIVAL

Evidence suggests that the main function of autophagy in cancer cells is to augment stress response resilience, therefore promoting tumor cell survival. Studies demonstrates that suppressing critical autophagy-related genes in neoplastic cells might induce or enhance cellular apoptosis. Cancer cells, owing to their rapid proliferation, exhibit increased metabolic demands, and *in vivo* studies indicate that, metabolic stress adversely affects the survival of cells without autophagy in comparison to those with autophagy competent ones. Autophagy may be triggered by cytotoxic and metabolic stresses, including hypoxia or nutritional deficiencies, to recycle ATP and support biosynthesis and cell survival. In hypoxic tumor cells, which are located away from blood vessels, autophagy is activated through both HIF-1α-dependent and independent mechanisms[19]. Inhibiting autophagy has been shown to improve the effectiveness of anticancer therapies, highlighting its protective role in tumor cells. Recent research has shown human cancer cell lines with activating mutations in H-ras or K-ras have increased autophagy levels. In these cells, blocking key autophagy-related proteins has been found to hinder cell growth, underscoring the importance of autophagy for tumor survival[20]. This indicates that targeting autophagy in Ras-driven cancers, where it plays a crucial role, could be a promising therapeutic approach.

5. THE ROLE OF AUTOPHAGY IN INDUCING CELL DEATH

Autophagy, while mostly acknowledged for its cytoprotective role, has also been suggested as a process of cellular demise, particularly when autophagic characteristics have been noted in cells undergoing death. This type of autophagy, associated with non-apoptotic cell death, has been seen in cancer cells. Chronic stress and extended autophagy may result in celldeath, if the breakdown of proteins and organelles surpasses the cell's regenerative abilities. The influence of autophagy-induced cell death in response to anticancer drugs seems contingent upon the particular cellular classification and genetic factors. STF-62247, a novel small-molecule drug, has shown the capacity to trigger apoptosis in renal cell carcinoma cells lacking VHL via enhancing autophagy. Nevertheless, in vivo data is less, and it remains uncertain whether autophagy-mediated cell death can be efficiently used for cancer treatment.

6. CELL SENESCENCE AND AUTOPHAGY

Autophagy and Senescence is a specific cellular stress response that functions as a tumor suppressor. Recent findings indicate that autophagy may facilitate senescence triggered by the Ras oncogene[21]. Cellular senescence refers to a sustained Cell cycle arrest is induced by inhibitors in metabolically active cells. Senescence may be induced by several methods, including oncogenes, DNA damage, and oxidative stress, including the active p53 and Rb tumor suppressor genes enhancing this process[22]. Senescence may contribute to autophagy-induced tumor dormancy. Furthermore, the suppression of autophagy in neoplastic cells has been shown to delay the development of senescence. During senescence, certain autophagy-related genes (ULK1 and ULK3) are increased, and the overexpression of ULK3 has been shown to enhance both autophagy and senescence[23].

7. AUTOPHAGY INDUCERS

Conventional cytotoxic agents and radiation have been shown to induce autophagy. Anticancer drugs recognized for their capacity to induce autophagy include imatinib, a BCR-ABL tyrosine kinase inhibitor; cetuximab, an anti-EGFR antibody; proteasome inhibitors; TRAIL; and HDAC inhibitors, such as vorinostat and OSU-HDAC42. Arsenic trioxide has shown the capacity to augment autophagy in leukemia and glioma cells via regulating the mitochondrial stress sensor BNIP3, particularly in malignant gliomas[24]. Furthermore, pharmacological agents using diverse methodologies, such as Tamoxifen, cyclooxygenase inhibitors, and the protease inhibitor nelfinavir, have shown the capacity to stimulate autophagy in neoplastic cells[25]. The ramifications of inducing autophagy in malignant cells persist largely elucidated, since the results are contingent upon variables such as the degree, length, and cellular environment. Excessive or extended autophagy could result in tumor cell death, though its role in vivo is still uncertain. mTOR is a crucial regulator of cellular growth, contributing substantially to protein synthesis and the regulation of autophagy. Rapamycin, a natural Allosteric mTOR inhibitors and their analogs (temsirolimus, everolimus,

deforolimus), specifically targets mTORC1 to enhance autophagy[26]. Despite their effectiveness in treating renal cell carcinoma, neuroendocrine tumors and lymphoma demonstrate poor treatment efficacy with rapamycin and its analogs (rapalogs) in other malignancies. One reason is that rapamycin does not inhibit mTORC2 and fails to disrupt the S6KIRS1 negative feedback loop, leading to AKT activation[27]. Preclinical investigations indicate that these dual mTORC1/mTORC2 inhibitors show antitumor activity and induce autophagy more effectively than mTORC1 inhibitors alone. For instance, PI-103, a dual PI3K-mTOR inhibitor, activated Autophagy in glioma cells, coupled with the use of autophagy inhibitors with PI-103, increased apoptosis. Moreover, NVP-BEZ235, currently in clinical trials, exhibited synergistic effects with chloroquine in glioma xenografts, promoting apoptosis[28]. The exact role of autophagy in the efficacy of these dual inhibitors remains unclear. The antidiabetic drug metformin can inhibit mTOR signaling via AMPK activation and has shown cytostatic effects in some cancer cells. Although metformin induces in colon cancer cells, it prevented autophagy triggered by 2-deoxyglucose in prostate cancer cells, reduced Beclin 1 levels, and shifted the response from survival to cell death, which challenges the expected autophagy activation by AMPK. Other autophagy-inducing agents include fluoxetine, maprotiline, and valproic acid. Screening assays have also identified the antihypertensive medications verapamil, minoxidil, and clonidine as autophagy stimulators through a calpain-dependent, mTOR-independent pathway[29].

8. AUTOPHAGY INHIBITORS

Several studies have shown that inhibiting autophagy, either through genetic manipulation of autophagy-related genes (Atgs) or by using pharmacological agents, can significantly boost apoptosis of neoplastic cells induced by several oncological therapies in preclinical models. Specifically, blocking autophagy in these models increased tumor cell sensitivity to alkylating agents. In leukemia, among colon cancer cell lines with impaired apoptosis, a decrease in autophagy was shown to increase the vulnerability of cells resistant to TRAIL-induced apoptotic treatment. Moreover, the suppression of autophagy significantly enhanced apoptosis. Cetuximab is a monoclonal antibody that specifically targets the Epidermal growth factor receptor (EGFR)[30]. Bafilomycin A1 preferentially inhibits vacuolar ATPase, while monensin and chloroquine/hydroxychloroquine function as lysosomotropic agents, preventing the acidification needed for the digestive enzymes in lysosomes to function properly[31]. Drugs like Taxanes, nocodazole, colchicine, and vinca alkaloids damage microtubules. Autophagy inhibitors that impair the destruction of autophagosomes involves the tricyclic antidepressant clomipramine in conjunction with the anti-parasitic drug lucanthone. Animal studies have established that, autophagy inhibition enhances chemosensitivity and induces tumor remission. In a Myc-driven murine lymphoma model, chloroquine (CQ) was used to inhibit autophagy resulted in an increase in tumor cell death mediated by cyclophosphamide, analogous to the effects seen with shRNA-mediated Atg5 knockdown, and also extended the duration before recurrence of the tumor[32]. In a colon cancer xenograft model, the amalgamation of chloroquine and vorinostat yielded in a substantial decrease in tumor burden and enhanced apoptosis. In prostate cancer xenograft models, CQ improved the therapeutic effectiveness of the Src inhibitor saracatinib which alone reduced tumor growth compared to control groups, while the combination with CQ further decreased tumor proliferation[33]. This combinatorial therapy yielded a minimum twofold augmentation in apoptotic tumor cells, indicating that autophagy inhibition facilitates apoptosis. Moreover, the use of 3-methyladenine to suppress autophagy enhanced the apoptosis triggered by 5-fluorouracil, linked to regression of tumors in colon cancer xenografts. Research suggests that the suppression of autophagy may enhance the efficacy of chemotherapeutic drugs via many cellular mechanisms. Among the several autophagy inhibitors, only CQ and hydroxychloroquine (HCQ) are notable are notable and have undergone evaluation in human trials, owing to their prevalent use in treating malaria and autoimmune disorders. Both medications can penetrate the blood-brain barrier, with hydroxychloroquine being favored in clinical settings due to its better side-effect profile. Encouraged by preclinical data, numerous Phase I/II studies are now examining the combination of HCQ with cytotoxic agent therapy across several cancer types. Nevertheless, obstacles remain, for HCQ's the extended half-life The need for micromolar quantities to successfully inhibiting autophagy may restrict its use in human investigations. A phase I study assessed hydroxychloroquine in conjunction with adjuvant temozolomide radiotherapy in glioblastoma patients, determining 600 mg per day as the highest tolerable dosage of HCQ, which attained quantities requisite for autophagy inhibition seen in prior research[34]. The results of the biomarker analysis indicate the possibility of autophagy monitoring regulation throughout treatment and associating these changes with clinical outcomes. Autophagy facilitates the breakdown of intracellular proteins via lysosomes and the ubiquitin-proteasome pathway. Considering the critical functions of both routes in protein degradation, it is suggested that their simultaneous blockage may provoke ER stress-related cytotoxicity owing to the buildup of unfolded protein aggregates, potentially activating autophagy via the JNK or PERK/eIF2a pathways[35]. The synergistic effect of the proteasome, the combination of the inhibitor bortezomib and CQ has shown a more pronounced decrease in tumor development, than the treatment of each drug separately in colon cancer xenografts.

9. RELATIONSHIP BETWEEN AUTOPHAGY AND APOPTOSIS

Inhibition of autophagy has been shown to augment apoptosis in neoplastic cells, that have functional apoptotic signaling pathways. While inhibition of apoptosis is frequently observed in human tumors, cancer cells under stress often resort to alternative cell death mechanisms. Although autophagy can serve as an alternative pathway for the specific circumstances, the mechanisms aaand the processes are inadequately defined. A multifaceted connection occurs between autophagy and apoptosis at various phases, since both processes use similar mediators, including essential equipment and upstream regulators. Recent study has shown a relationship between autophagy and the extrinsic apoptotic pathway, via the regulation of p62/SQSTM1. This protein interacts with caspase-8, promoting its aggregation and activation, hence augmenting TRAIL-induced apoptosis. PATH, a cytokine recognized for its ability to trigger apoptosis in several tumor types, is now being assessed the processes of cell death in apoptosis-resistant cells are inadequately defined[36]. A multifaceted connection occurs between autophagy and apoptosis at various phases. is often seen in several cancers, promoting both intrinsic and extrinsic resistance to therapies.

10. AUTOPHAGY AS A THERAPEUTIC TARGET

Autophagy is crucial for tumor suppression, and its activation may serve as a vital technique for the prevention of cancer. The combination of the inhibitor bortezomib and CQ has shown a more significant reduction in tumor progression compared to the administration of each medication individually in colon cancer xenografts (6). Current Phase I/II clinical studies are investigating this combination in patients with relapsed or refractory multiple myeloma. An additional study found that metformin's inhibition of mTOR signaling decreased carcinogenesis in tumor model37. Moreover, sustained the injection of modest doses of Rapamycin in APCMin/+ mice, who have elevated AKT-mTOR signaling, significantly reduced intestinal neoplasia[38]. Inadequate autophagy has been associated with the onset of colonic cancers, mostly due to the abnormal activation of signaling caused by autophagy. The exploration of additional pharmacological agents that activate autophagy could be beneficial for cancer chemoprevention, warranting further investigation.

11. CONCLUSION

Autophagy serves dual roles in cancer biology; it acts serving as a tumor suppression mechanism while simultaneously acting as a flexible stress response in neoplastic cells, facilitating their survival under increased metabolic circumstances demanding, low oxygen levels, or during cancer therapies. This autophagy-mediated survival may contribute to the progression of developed neoplasms. Preclinical investigations suggest that stress-induced autophagy primarily provides cytoprotection to tumor cells, suggesting that, inhibiting this process could enhance the effectiveness of various anticancer treatments by promoting tumor cell death. As a result, autophagy emerges as a promising therapeutic target, opening new possibilities for cancer treatment strategies. While several medicines may impede autophagy, many are deficient in specificity and effectiveness for cancer treatment. CQ has undergone comprehensive evaluation in preclinical settings, especially in patients with solid malignancies. Exploring the function of autophagy in cancer offers distinct prospects for pharmaceutical innovation, due to the pressing need for more effective and selective autophagy inhibitors. Furthermore, the progression of biomarkers for evaluating autophagy modification during therapy should be a primary objective of drug development initiatives. Notwithstanding significant progress, numerous critical concerns remain, including the control of autophagy in tumor cells, the interaction the relationship the relationship between autophagy and apoptosis, as well as the mechanisms via which autophagy promotes treatment resistance. Acquiring a more profound comprehension of autophagy within the framework of cancer is crucial for leveraging its potential therapeutic advantages. Additionally, considering autophagy's role in tumor suppression, its activation could represent a significant strategy for cancer chemoprevention.

12. AUTHORS CONTRIBUTION STATEMENT

Study conception and design: Dr. Anand Mohan Jha, Dr. Anil Kumar; Data collection: Dr. Kumud Kumari, Dr. Rashmi Hosamani; Analysis and interpretation of results: Dr. S. Ravichandran, Dr. Vanitha Innocent Rani; Draft manuscript preparation: Dr Priyanka Singh. All authors reviewed the results and approved the final version of the manuscript.

13. CONFLICT OF INTEREST

Conflict of interest declared none.

14. REFERENCES

1. Ryter SW, Cloonan SM, Choi AM. Autophagy: a critical regulator of cellular metabolism and homeostasis. Molecules and cells. 2013 Jul 1;36(1):7-16.
2. Tai H, Wang Z, Gong H, Han X, Zhou J, Wang X, Wei X, Ding Y, Huang N, Qin J, Zhang J. Autophagy impairment with lysosomal and mitochondrial dysfunction is an important characteristic of oxidative stress-induced senescence. Autophagy. 2017 Jan 2;13(1):99-113.
3. Qu X, Yu J, Bhagat G, Furuya N, Hibshoosh H, Troxel A, et al. Promotion of tumorigenesis by heterozygous disruption of the beclin 1 autophagy gene. J Clin Invest 2003;112:1809–20.
4. Maiuri MC, Zalckvar E, Kimchi A, Kroemer G. Self-eating and selfkilling: crosstalk between autophagy and apoptosis. Nat Rev Mol Cell Biol 2007;8:741–52.
5. Duffy A, Le J, Sausville E, Emadi A. Autophagy modulation: a target for cancer treatment development. Cancer chemotherapy and pharmacology. 2015 Mar;75:439-47.
6. Li W, Zhang L. Regulation of ATG and autophagy initiation. Autophagy: Biology and Diseases: Basic Science. 2019:41-65.
7. Pankiv S, Clausen TH, Lamark T, Brech A, Bruun JA, Outzen H, et al. p62/SQSTM1 binds directly to Atg8/LC3 to facilitate degradation of ubiquitinated protein aggregates by autophagy. J Biol Chem 2007; 282:24131–45.
8. Ng EL, Gan BQ, Ng F, Tang BL. Rab GTPases regulating receptor trafficking at the late endosome–lysosome membranes. Cell biochemistry and function. 2012 Aug;30(6):515-23.
9. Ballesteros-Álvarez J, Andersen JK. mTORC2: The other mTOR in autophagy regulation. Aging cell. 2021 Aug;20(8):e13431.
10. Karabi Z, Moradian F, Kheirabadi M. The effect of lactoferrin on ULK1 and ATG13 genes expression in breast cancer cell line MCF7 and bioinformatics studies of protein interaction between lactoferrin and the autophagy initiation complex. Cell Biochemistry and Biophysics. 2022 Dec;80(4):795-806.
11. Tian W, Li W, Chen Y, Yan Z, Huang X, Zhuang H, Zhong W, Chen Y, Wu W, Lin C, Chen H. Phosphorylation of ULK1 by AMPK regulates translocation of ULK1 to mitochondria and mitophagy. FEBS letters. 2015 Jul 8;589(15):1847-54.
12. Papandreou I, Lim AL, Laderoute K, Denko NC. Hypoxia signals autophagy in tumor cells via AMPK activity, independent of HIF-1, BNIP3, and BNIP3L. Cell Death & Differentiation. 2008 Oct;15(10):1572-81.
13. Yue Z, Jin S, Yang C, Levine AJ, Heintz N. Beclin 1, an autophagy gene essential for early embryonic development, is a haploinsufficient tumor suppressor. Proceedings of the National Academy of Sciences. 2003 Dec 9;100(25):15077-82.

14. Wang Y, Zhang N, Zhang L, Li R, Fu W, Ma K, Li X, Wang L, Wang J, Zhang H, Gu W. Autophagy regulates chromatin ubiquitination in DNA damage response through elimination of SQSTM1/p62. Molecular cell. 2016 Jul 7;63(1):34-48.
15. Divya T, Sureshkumar A, Sudhandiran G. Autophagy induction by celastrol augments protection against bleomycin-induced experimental pulmonary fibrosis in rats: Role of adaptor protein p62/SQSTM1. Pulmonary Pharmacology & Therapeutics. 2017 Aug 1;45:47-61.
16. Tang D, Kang R, Livesey KM, Cheh CW, Farkas A, Loughran P, Hoppe G, Bianchi ME, Tracey KJ, Zeh III HJ, Lotze MT. Endogenous HMGB1 regulates autophagy. Journal of Cell Biology. 2010 Sep 6;190(5):881-92.
17. Ying H, Qu D, Liu C, Ying T, Lv J, Jin S, Xu H. Chemoresistance is associated with Beclin-1 and PTEN expression in epithelial ovarian cancers. Oncology letters. 2015 Apr 1;9(4):1759-63.
18. Heras-Sandoval D, Pérez-Rojas JM, Hernández-Damián J, Pedraza-Chaverri J. The role of PI3K/AKT/mTOR pathway in the modulation of autophagy and the clearance of protein aggregates in neurodegeneration. Cellular signalling. 2014 Dec 1;26(12):2694-701.
19. Zhao Y, Chen G, Zhang W, Xu N, Zhu JY, Jia J, Sun ZJ, Wang YN, Zhao YF. Autophagy regulates hypoxia-induced osteoclastogenesis through the HIF-1α/BNIP3 signaling pathway. Journal of cellular physiology. 2012 Feb;227(2):639-48.
20. RASHMI BA, HARISHCHANDER A, SIVARAMAN T. AN OUTLOOK ON DRUGGABLE TARGETS TO COMBAT PANCREATIC DUCTALADENOCARCINOMA. SPECIAL ISSUE ON.:98.
21. Lock R, Roy S, Kenific CM, Su JS, Salas E, Ronen SM, Debnath J. Autophagy facilitates glycolysis during Ras-mediated oncogenic transformation. Molecular biology of the cell. 2011 Jan 15;22(2):165-78.
22. Larsson LG. Oncogene-and tumor suppressor gene-mediated suppression of cellular senescence. InSeminars in cancer biology 2011 Dec 1 (Vol. 21, No. 6, pp. 367-376). Academic Press.
23. Wong PM, Puente C, Ganley IG, Jiang X. The ULK1 complex: sensing nutrient signals for autophagy activation. Autophagy. 2013 Feb 28;9(2):124-37.
24. Kanzawa T, Zhang L, Xiao L, Germano IM, Kondo Y, Kondo S. Arsenic trioxide induces autophagic cell death in malignant glioma cells by upregulation of mitochondrial cell death protein BNIP3. Oncogene. 2005 Feb;24(6):980-91.
25. Banga R, Banga V, Eltalla A, Shahin L, Parag S, Naim M, Iyer E, Kumrah N, Zacharias B, Nathanson L, Beljanski V. Effects of autophagy modulators tamoxifen and chloroquine on the expression profiles of long non-coding RNAs in MIAMI cells exposed to IFNγ. Plos one. 2022 Apr 21;17(4):e0266179.
26. Wu L, Feng Z, Cui S, Hou K, Tang L, Zhou J, Cai G, Xie Y, Hong Q, Fu B, Chen X. Rapamycin upregulates autophagy by inhibiting the mTOR-ULK1 pathway, resulting in reduced podocyte injury. PloS one. 2013 May 8;8(5):e63799.
27. Alves CL, Ditzel HJ. Drugging the PI3K/AKT/mTOR pathway in ER+ breast cancer. International Journal of Molecular Sciences. 2023 Feb 24;24(5):4522.
28. Maity A, Cerniglia GJ, Karar J, Koumenis C. Inhibition of autophagy as a strategy to augment radiosensitization by the dual PI3K/mTOR inhibitor NVP-BEZ235. International Journal of Radiation Oncology, Biology, Physics. 2012 Nov 1;84(3):S127.
29. Williams A, Sarkar S, Cuddon P, Ttofi EK, Saiki S, Siddiqi FH, Jahreiss L, Fleming A, Pask D, Goldsmith P, O'kane CJ. Novel targets for Huntington's disease in an mTOR-independent autophagy pathway. Nature chemical biology. 2008 May;4(5):295-305.
30. Harding J, Burtness B. Cetuximab: an epidermal growth factor receptor chemeric human-murine monoclonal antibody. Drugs of today (Barcelona, Spain: 1998). 2005 Feb 1;41(2):107-27.
31. Harada M, Sakisaka S, Yoshitake M, Kin M, Ohishi M, Shakado S, Mimura Y, Noguchi K, Sata M, Tanikawa K. Bafilomycin A1, a specific inhibitor of vacuolar-type H+-ATPases, inhibits the receptor-mediated endocytosis of asialoglycoproteins in isolated rat hepatocytes. Journal of hepatology. 1996 May 1;24(5):594-603.
32. Ferrao PT, Bukczynska EP, Johnstone RW, McArthur GA. Efficacy of CHK inhibitors as single agents in MYC-driven lymphoma cells. Oncogene. 2012 Mar;31(13):1661-72.
33. Edwards J. Src kinase inhibitors: an emerging therapeutic treatment option for prostate cancer. Expert opinion on investigational drugs. 2010 May 1;19(5):605-14.
34. Rosenfeld MR, Ye X, Supko JG, Desideri S, Grossman SA, Brem S, Mikkelson T, Wang D, Chang YC, Hu J, McAfee Q. A phase I/II trial of hydroxychloroquine in conjunction with radiation therapy and concurrent and adjuvant temozolomide in patients with newly diagnosed glioblastoma multiforme. Autophagy. 2014 Aug 20;10(8):1359-68.
35. Kim SH, Kwon D, Lee S, Ki SH, Jeong HG, Hong JT, Lee YH, Jung YS. Polyhexamethyleneguanidine phosphate-induced cytotoxicity in liver cells is alleviated by tauroursodeoxycholic acid (TUDCA) via a reduction in endoplasmic reticulum stress. Cells. 2019 Sep 3;8(9):1023.
36. Jung KT, Oh SH. Polyubiquitination of p62/SQSTM1 is a prerequisite for Fas/CD95 aggregation to promote caspase-dependent apoptosis in cadmium-exposed mouse monocyte RAW264. 7 cells. Scientific Reports. 2019 Aug 22;9(1):12240.
37. Amin S, Lux A, O'Callaghan F. The journey of metformin from glycaemic control to mTOR inhibition and the suppression of tumour growth. British journal of clinical pharmacology. 2019 Jan;85(1):37-46.
38. Koehl GE, Spitzner M, Ousingsawat J, Schreiber R, Geissler EK, Kunzelmann K. Rapamycin inhibits oncogenic intestinal ion channels and neoplasia in APCMin/+ mice. Oncogene. 2010 Mar;29(10):1553-60.